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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/782,401	02/19/2004	Philip Ashton-Rickardt	ARCD:390US	4307

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/782,401	ASHTON-RICKARDT, PHILIP	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) *3-5* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,12-17,21-23,25-31,33,35-37,39,40,46,49-52,56,61,63,64 and 205* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/24/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 1-6,12-17,21-23,25-31,33,35-37,39,40,46,49-52,56,61,63,64 and 205.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 1/24/2007 in response to the previous Non-Final Office Action (10/02/2006) is acknowledged and has been entered.

Claims 1-6, 12-17, 21-23, 25, 26-31, 33, 35-37, 39-40, 46, 49-52, 56, 61, 63-64 and 205 are currently pending.

Claims 3-5 are withdrawn from consideration as being drawn to non-elected inventions.

Claim 1-2, 6, 12-17, 21-23, 25, 26-31, 33, 35-37, 39-40, 46, 49-52, 56, 61, 63-64 and 205 are currently under consideration.

The Declaration under 37 CFR 1.132 filed by Dr. Raymond Welsh on 1/24/2007 is insufficient to overcome the rejection of claims 1, 29-31, 33, 35-37, 39-46, 49-52, 56, 59, 61 and 63-64 based upon under 35 U.S.C. 112, first paragraph, as set forth in the last Office action because the declaration does not appear to be commensurate in scope with the claimed invention. For example, the Declaration clearly sets forth that LCMV infection in mice, as described in the specification, is a model for many human diseases associated with T cell-mediated immunopathology, where in such diseases include, but are not limited to, diseases associated with increased lysosomal permeability, diseases associated with autophagic cell death, diseases associated with cell death mediated by TNF-a, diseases associated with reactive oxygen species, and diseases associated with necrosis. The Declaration further provides a number of references which support the correlation between LCMV and different diseases and states that "[B]ased on my review of these materials and my experience, a skilled virologist with an ordinary understanding of viral immunology would have understood, at the time the above referenced application was filed, that LCMV infection in mice is an established model for a wide variety of diseases associated with immunopathology in humans. Moreover, the Declaration provides a review of the instant specification and identifies the following sections pertaining to LCMV infection and in vivo studies:

- Page 65, lines 21-28 provides general information and guidance regarding generation of LCMV infection in mice.

- Example 3 (page 65, line 1-page 94, line 4) provides information regarding the identification of Spi2A as a protective gene that facilitates the differentiation of memory T lymphocytes using a LCMV mouse model.
- Further, in vivo studies demonstrate that expression of Spi2A increased the percentage and absolute number of anti-LCMV CD8 cells in Spi2A mice in two independent experiments.
- Examples 6, 7, 9, 11, 12, 13 and 14, provides general guidance regarding the establishment of clinical trials pertaining to the use of Spi2A polypeptides and Spi2A polypeptide equivalents for the treatment of cancer, septic shock, Alzheimer disease and liver diseases.

Moreover, the Declaration sets forth a review of a report by the inventors (Nature Immunology, 5(9): 919-926, 2004; "Exhibit 19") that provides information which supports the findings set forth in the application that Spi2A is a protective factor for memory T cell development. In particular, the Declaration teaches that the paper presents results of the studies showing that the gene encoding Spi2A is upregulated in memory cell precursors and that Spi2A upregulation protected LCMV-specific memory progenitors from programmed cell death. Thus, the Declaration concludes with "[I]n view of the information set forth in the specification pertaining to the protective role of Spi2A in facilitating the differentiation of memory T-lymphocytes and the state of the act pertaining to LCMV, it is my belief that a person of ordinary skill in the my field would understand that Spi2A will be a benefit in abrogating immunopathology associated with LCMV infection"; and therefore, in view of the specification, would be able to practice the invention as claimed without undue experimentation.

Thus, while the declaration has clearly set forth that the LCMV infection in mice, as described in the specification, is an art recognized model for many human diseases associated with T cell-mediated immunopathology; and further, that Spi2A has a protective role in facilitating the differentiation of memory T-lymphocytes as evidenced by the upregulation of Spi2A protection of LCMV-specific memory progenitors from programmed cell death (emphasis added), the Examiner recognizes that the present invention is drawn to a method of modulating cell death in a cell comprising contacting said cell with a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein cell death is modulate. As such, the claims broadly encompass an in vitro,

as well as in vivo, method of modulating cell death comprising administering a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein the cell is in a subject, e.g. in vivo, and not to expressing Spi2A in vivo (emphasis added). Thus, while the specification provides seven prophetic examples to establish clinical trials pertaining to the use of Spi2A polypeptides and Spi2A polypeptide equivalents for the treatment of cancer, septic shock, Alzheimer disease and liver diseases, the specification appears to be silent on any correlation between the in vitro testing and in vivo success, e.g. administration of a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein cell death is modulated in the cell.

Information Disclosure Statement

The Information Disclosure Statement filed on 1/24/2007 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. A signed copy of the IDS's are attached hereto.

New rejections necessitated by Amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 6, 12-17, 21-23, 25, 26-31, 33, 35-37, 39-40, 46, 49-52, 56, 61, 63-64 and 205 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In Wands, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (Wands, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of Wands factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims are drawn to a method of modulating cell death in cell comprising contacting said cell with a polypeptide, wherein cell death is modulated in the cell. The invention is in a class of

invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of modulating cell death in a cell comprising contactign said cell with a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein cell death is modulated in the cell. The claims are further drawn to said cell being in a subject such as a human and the subject has a variety of diseases including, but not limited to, hepatic failure, an inflammatory disease, a vascular disease, cancer, a bone disease, a viral infection, an autoimmune disease, multiple sclerosis or arthritis. Thus, the claims encompass a method of modulating cell death both in vitro, as well as, in vivo comprising administering a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein cell death is modulated.

Guidance in the specification and Working Examples

The specification teaches that Spi2A inhibits both the caspase pathway and caspase-independent pathway of cell death (page 5, lines 9-10). For example, the specification teaches that Spi2A protects from apoptosis, wherein the activation of both apical and executioner caspases, as well as Bid, was suppressed in RelA-/- MEFs that expressed high levels of Spi2A (page 59, 2nd full paragraph). The specification further (page 60, lines 4-16) teaches that Spi2A inhibited both serine and cysteine proteases, similar to serpin, SQN-5 and also, inhibited the chymotrypsin-like, serine protease cathepsin G, but not elastase or either granzyme B or granzyme A. Moreover, the specification provides an example of Spi2A inhibition of caspase-independent cell death, wherein NIH3T3 cells were transduced with MIGR1 retrovirus encoding either rGFP alone or Spi2A in the forward (sense) or reverse (antisense) orientation (page 61, Example 2). In addition, the specification contemplates the in vivo prevention of tumor development using Spi2A polypeptides (page 95, Example 6), the treatment of myocardial infarction in human subjects (page 96, Example 7), the treatment of septic shock in human subjects (Example 8), the treatment of cancer (page 98,

Example 9) and the clinical trials using Spi2A polypeptides in the treatment of diseases in general (page 100, example 11). Thus, while the specification provides a variety of in vitro test cells transduced with a retrovirus encoding Spi2A, as well as contemplates in vivo use, the specification appears to be silent on any correlation between the in vitro testing which involves the use of a polypeptide of SEQ ID NO: 2 or fragments thereof and in vivo use. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Quantity of experimentation

The quantity of experimentation in the areas of in vivo use such as for cancer therapy is extremely large given the unpredictability associated with treating cancer in general and the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize that there are eleven human cathepsins which are located within lysosomes, wherein TNF-R1 has been found to trigger cell death independently of caspases by causing lysosomes to release cathepsin B into the cytoplasm. For example, Foghsgaard et al. (J. Cell Biology 2001; 153: 999-1009, *of record*) teach that cathepsin B inhibitors such as cystatin A and an antisense-mediated depletion of cathepsin B rescued WEHI-S cells from apoptosis triggered by TNF or TNF-related apoptosis-inducing ligand (abstract). Moreover, Foghsgaard et al. teach that cathepsin B acts as an essential downstream mediator of TNF-triggered and caspase-initiated apoptosis cascade. With regards to serpins, those of skill in the art at the time the invention was filed would recognize that the serpin family of protease inhibitors have a well established place in control of extracellular proteolytic cascades, wherein two, human protease inhibitor 6 (PI-6) and PI-9, have recently been found to regulate the intracellular proteases Cathepsin G and granzyme B, as taught by Morris et al. (Biochem. J. 2003; 371: 165-173, *of record*). Morris et al. further teach that murin serpin 2A, e.g., Spi2A, has also been found to be localized both

in the cytoplasm and the nucleus of the cell and suggest that the biological activities of the protein will be modulated by cellular redox conditions (page 166, 1st column, 1st full paragraph). However, Morris et al. teach that the function of intracellular serpins has largely been inferred from their *in vitro* interaction with target proteases and that there is little evidence to tell us whether their activity is regulated or to explain the significance of the redox-sensitive residues around the reactive site (page 165, 2nd column, paragraph briding 1st column). Thus, while considerable research has gone into to identifying the in vitro function of serpins, one of skill in the art would recognize that a considerable amount of in vitro empirical testing is required, with no *a priori* expectation of success being present, before serpin 2a, e.g., Spi2A can be considered useful for a disease state.

With regards to the unpredictability in the art, those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4, *of record*) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320, *of record*) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. In addition, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step

that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Moreover, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042, *of record*) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the lack of guidance provided in the specification for correlation in vitro results to in vivo success, and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Note: In order to expedite prosecution, the Examiner would like to address Applicants arguments pertaining to the previous rejection as they relate to the instant rejection. In response to the previous rejection, Applicants assert that the specification sets forth in vitro studies demonstrating that Spi2A protects cells from apoptosis. For example, Applicants assert that Example 1 shows an in vitro study which demonstrates that the induction of Spi2A by NF-kB protects cells from TNF-□ mediated cell death, apoptosis and the lysosomal pathway of cell death. Moreover, Applicants assert that contrary to the Examiners position, the specification is not silent on a correlation between in

vitro results and in vivo data. In particular, Applicants submit that the specification teaches studies demonstrating that Spi2A determines the level of antigen-specific CD8 cells after infection of the mouse with LCMV (see specification, page 89, line 17 to page 91, line 2). Moreover, Applicants assert that the specification sets forth data demonstrating that expression of Spi2A increased the percentage and absolute number of anti-LCMV CD8 cells in Spi2A mice in two independent experiments (page 91, line 4 to page 93, line 9, Figures 19-20 and Table 7); and further, sets forth in vivo studies demonstrating that Spi2A affects the potency of recall response to LCMV (specification, page 93, line 11 to page 94, line 4). As such, Applicants assert that these finding are consistent with the in vitro studies because they establish that Spi2A has an effect on memory cell differentiation and the escape of memory cells from programmed cell death. Applicants further assert that the LCMV mouse is an established model for disease in humans, as evidenced by the Declaration of Dr. Raymond M. Welsh (Exhibit A; hereinafter the "Declaration"). Specifically, Applicants assert that the Dr. Welsh has declared that "[a] skilled immunologist with an ordinary understanding of immunology would have recognized, at the priority date of the Application, that LCMV infection in mice is a model for many diseases associated with T cell-mediated immunopathology." In support of this statement, Applicants assert that Dr. Welsh cites a plethora of literature relevant to LCMV which would be familiar to one having an ordinary understanding of immunology and virology. In addition, Applicants assert that Dr. Welsh has reviewed a publication of the inventors after the priority date of the present application, Nature Immunology, 5(9): 919-926, 2004) that shows that the gene encoding Spi2A is upregulated in memory cell precursors; and states that the inventors publication provides evidence supporting the benefit of Spi2A in inducing T-cell mediated immunity in vivo. Thus, in view of the information set forth above pertaining to the in vitro and in vivo data set forth in the specification, the substantial information known in the art regarding Spi2A and the LCMV mouse and a model for human disease, one of ordinary skill in the art, being highly skilled, would be able to practice the invention without undue experimentation. With regards to the state of the prior art, Applicants assert the instant invention is directed to understanding the in vivo effects of serpins, wherein as set forth in the specification and further detailed in the Liu et al. reference, the present inventors have found that Spi2A functions to promote memory cell survival and development. In particular, Applicants point to the in vivo

studies in the LCMV mouse set forth in the specification which appears to be overlooked by the Examiner.

These arguments have been carefully considered, but are not found persuasive.

First, regarding Applicants assertions that the specification sets forth in vitro studies demonstrating that Spi2A protects cells from apoptosis, the Examiner acknowledges that the specification teaches in vitro data showing that induction of Spi2A by NF-kB protects cells from TNF-a mediated cell death, apoptosis, and the lysosomal pathway of cell death (Example 1); and further provides examples demonstrating that Spi2A protects cells from caspase-independent lysosomal pathway of cell death, and cell death due to reactive oxygen species. However, the Examiner recognizes that each of the examples appear to induce Spi2A via transduction of retroviruses encoding Spi2A, i.e. expression of Spi2A, which does not appear to be commensurate in scope with the claimed invention which involves contacting a cell with a polypeptide of SEQ ID NO: 2 or fragments thereof, wherein cell death of the cell is modulated. Next, the majority of Applicants arguments appear to revolve around the *in vivo* studies in the LCMV mouse set forth in the specification and the submission of the Welsh declaration for support that the LCMV mouse is an established model for disease in humans. Thus, while the Examiner concedes that the LCMV mouse model is an established model for a variety of diseases in humans, these arguments, as well as the Declaration, do not appear to be commensurate in scope with the claimed invention. In other words, while the Declaration clearly sets forth that LCMV mouse model is an established model for disease in human and the specification teaches that expression of Spi2A increased the percentage and absolute number of anti-LCMV CD8 cells in Spi2A mice in two independent experiments, the present invention is drawn to a method of modulating cell death in a cell comprising contacting said cell with a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein cell death is modulate. As such, the claims broadly encompass an in vitro, as well as in vivo, method of modulating cell death comprising contacting/administering a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein the cell is in a subject, e.g. in vivo, and not to expressing Spi2A in vivo (emphasis added). Thus, while the specification provides seven prophetic examples to establish clinical trials pertaining to the use of Spi2A polypeptides and Spi2A polypeptide equivalents for the treatment of cancer, septic shock, Alzheimer disease and liver diseases, the specification appears to be silent on any correlation between in vitro testing and in vivo

success, e.g. administration of a polypeptide comprising at least 5 consecutive amino acids of SEQ ID NO: 2, wherein cell death is modulated in the cell. As such, if there is no correlation then the examples do not constitute working examples. While it is understood that the absence of working examples should never be the sole reason for rejecting a claims as being broader than an enabling disclosure, the criticality of working examples in an unpredictable art, such as the treatment of cancer, is required for practice of the claimed invention.

Therefore, No claim is allowed.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BF

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